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10/500,530	02/16/2005	Cindy Castado	B45292	7712

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,530	CASTADO ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-96* is/are pending in the application.

4a) Of the above claim(s) *68-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAIL ACTION

Applicant's cancellation of claims 31-59 and introduction of new claims 60-96 in response filed on 02-22-2006, in response to the Requirements for Restriction is acknowledged. Applicant election of Group I, drawn to an polypeptide of SEQ ID NO. 2 and derivatives thereof (i.e., newly presented claims 60-67) in response to the Requirements for Restrictions is acknowledged. The examiner understand that election of SEQ ID No. 1 is withdrawn for further prosecution on the merits as drawn to a cancelled claim 31.

Applicant's election of Group I in the reply filed on 02-22-2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and made Final.

Claims 60-96 are pending in the instant application. Claims 68-96 are withdrawn from further consideration as drawn to non-selected species. Therefore, claims 60-67 are pending to which the following grounds of rejection are applicable.

Specification Informalities

Recitation of XL Fit software program, on page 67 is noted. However, the software programs can be readily changed with rapidly changing technology and therefore, may not be available to the public. Therefore, applicant is advised to amend the specification and use some other means to recite the program.

Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections

35 USC § 112- First paragraph- Written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 60-67 encompass a genus of unspecified variants of SEQ ID NO:2. Claim 1 recites (a) an isolated polypeptide having at least 99% identity to the polypeptide in SEQ ID NO:2, and (b) an immunogenic fragment of a least 15 contiguous aminoacids of SEQ ID NO:2. Claims 64-67 introduce a further limitation to a fusion protein. The gene or fragment of of SEQ ID NO:2 when given the broadest reasonable interpretation encompass a genus of unspecified variants of SEQ ID NO:2, which can elicit an immunogenic response when administered to a subject, inducing an antibody response that recognizes an epitope within SEQ ID NO:2. The specification and claims do not place any limits on the number of amino acid substitutions, deletions, and/or insertions that may be made to SEQ ID NO:2, and these variants need not to retain full or even partial immunological activity as embraced by the claims.

Applicant discloses in the specification the meaning of a fragment as "a polypeptide having an amino acid sequence that is entirely the same as part but not all of any amino acid sequence of any polypeptide of the invention. As with BASB231 polypeptides, fragments may be "free-standing," or comprised within a larger polypeptide of which they form a part or region, most preferably as a single continuous region in a single larger polypeptide. (p. 10, lines 28-30 bridging to p. 11, lines 1-2). Additionally, Applicant teaches preferred fragments as " truncation polypeptides having a portion of an amino acid sequence selected from SEQ Group 2 or of variants thereof. ... characterized by structural or functional attributes such as fragment that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions,

surface-forming regions, substrate binding region, and high antigenic index regions (p. 11, lines 4-14)".

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant provides cloning and characterization of

an isolated polypeptide of SEQ ID NO: 2, which is encoded by the BASB 231 gene from the nontypeable *Haemophilus influenzae* (*H. influenzae*) strain 3224A, ATCC PTA-1816. The specification teaches the full-length protein comprising 150 amino acids as set fort in SEQ.ID.NO: 2 and contemplates its use in diagnosing a nontypeable *H. influenzae* infection (p. 68, Example 7) and/or as a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae* (p. 68, Example 8). However, the immunological function of this gene or its product in assessing a nontypeable *Haemophilus influenzae* infection has not yet been identified. The as-filed specification does not teach regions or domains of the protein essential for immunological functions, other than the amino acid sequence of SEQ ID NO: 2. There is no disclosure of what amino acids are in active sites, the binding pocket or the hydrophobic core of the protein. There is no structure/function relationship taught at all for claimed variants and fragments other than the full length SEQ ID NO:2. Further, there is no teaching of how many amino acids may be deleted from either or both the N- and C-terminals and retain function.

Further, the specification does not disclose i) an isolated polypeptide comprising an amino acid sequence which has at least 99%, identity to SEQ.ID.NO: 2, ii) an immunogenic fragments of polypeptides comprising at least 15 amino acids of SEQ.ID.NO: 2 (the examiner considers these variants and hereafter will be referred to as variants) or fusion protein comprising said fragments (i.e., 15 amino acids) able to induce an immunological response characterized by its use in diagnosing a nontypeable *H. influenzae* infection (p. 68, Example 7) and/or as a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae.* This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, as one of skill in the art cannot envision all the fragments

having an immunological function as to be used in diagnosing a nontypeable *H. influenzae* infection and/or as a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae*, based on the teachings in the specification. Thus, it is not possible from reading the examples to envision what types of mutations have been introduced, how many mutations have been introduced in each modified SEQ ID NO:2 or which genes have incurred mutations to result in the claimed immunological activity. Further, the specification does not describe any use of said variants in identifying a nontypeable *H. influenzae.*

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., amino acid sequence), specific features and functional attributes (e.g., induction of immunological activity as to be used in diagnosing a nontypeable *H. influenzae* infection and/or as a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae* activity) that would distinguish different members of the claimed genus. Of note, inducing an immune response is not an identifying characteristic of a fragment because there are many fragments with the same function in a polypeptide and such variants are not distinguishable from each other.

Hence in the instant case, no other characteristic in addition to the functional discussed above are disclosed. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera form each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species

> which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Although sufficient description is given for a polypeptide having the amino acid sequence of SEQ ID NO:2, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of a SEQ ID NO:2, a variant, fragment or derivative thereof encoding a functional immunological activity in diagnosing a nontypeable *H. influenzae* infection and/or in a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae*. Therefore, said variants do not meet the guidelines on written description.

Additionally, claims 64-67 is rejected as failing to comply with the written description requirement. Claim 64 and dependent claims 65-67 recite a genus of unspecified fusion proteins. The specification discloses a number of species of the genus, on p. 13, lines 26-31 bridging to p. 14, lines 1-8, such as protein D from Haemophilus influenzae and the non-structural protein from influenza virus, NS1 (hemagglutinin), Omp26 (WO 97/01638), and LytA and the C terminal portion of the molecule. However applicant is silent about any structural features commonly possessed by members of the genus that distinguish them from other carrier or transport molecules selected as a coupling partner of an isolated polypeptide, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of unspecified fusion proteins.

Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112- First paragraph-Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make an/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites an isolated functional fragment of the SEQ ID NO:2 wherein one or more amino acids are deleted from the amino acid sequence of SEQ ID NO: 2. This invention utilizes disciplines of recombinant technology as well as protein production. As well, assays for "functional" fragments" among the recombinant molecules are required to perform the invention.

2) Scope of the invention. The fragments can have any number of deletions at the N-terminus or C-terminus. Therefore, claims 60-67 recite a broad collection of proteins.

3) Number of working examples and guidance. While the sequence of SEQ ID NO: 2 is taught in the specification, no examples of fragments of cloning of the BASB231 gene or what domains or regions are required to induced an immunological response to be used in diagnosing a nontypeable *H. influenzae* infection and/or in a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae* activity. Applicant contemplates immunogenic fragments of BASB231 "as the polypeptide comprising the corresponding amino acid sequence selected from SEQ Group 2; That is to say, the fragment (if necessary when coupled to a carrier) is capable of raising an immune response which recognizes the BASB231 polypeptide (or can perform the same enzymatic function as the BASB231 polypeptide). Such an immunogenic (or enzymatically functional) fragment may include, for example, the BASB231 polypeptide lacking an N-terminal leader sequence, and/or a transmembrane domain and/or a C-terminal anchor domain" (p. 10, lines 14-21). However, there is no indication of a structure-function relationship between the sequence of SEQ ID NO 2 and a nontypeable *Haemophilus influenzae* functional immune activity. Furthermore, the instant specification fails to demonstrate any examples or specific guidance for the identification or isolation of "functional fragments" of SEQ ID NO: 2, i.e. assays for the analysis of SEQ ID NO: 2 fragments that would meet the limitations of the claims. Applicants simply state that using methods known in the art specific for standard cloning and screening methods with reference to Maniatis, T., Fritsch, E. F. and Sambrook et al., MOLECULAR CLONING, A LABORATORY MANUAL, (p. 16, lines 7-110. This guidance, for the isolation, cloning and sequence analysis of SEQ ID NO: 1 gene coding for SEQ ID No. 2 is provided in the specification. However, no guidance is given for the isolation of "functional" fragments of SEQ ID No. 2 **protein**.

4) State of the art. Recombinant technology for the generation of new protein fragments is highly developed. However, the ability to determine *a priori* whether a mutation will generate a functional fragment is not. The art must therefore be considered to be poorly developed.

5) Unpredictability of the art. Without knowing the structure-function relationship of SEQ ID NO:2, the ability to predict the effect of mutations on function is highly unpredictable.

6) Amount of Experimentation Required. The invention recites isolated functional fragments of the polypeptide of SEQ ID NO: 2. In view of the unpredictability of the art of predicting the functional nature of fragments of SEQ ID NO 2 deleted of any number of amino acids from the C-terminus and/or the N-terminus: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/ functional characteristics of a protein from primary amino acid sequence alone, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

As such, and to the extent that the claimed invention is drawn to an isolated polypeptide fragment of SEQ ID NO: 2 or variant thereof with the intended use of eliciting a functional immune response to be used in diagnosing a nontypeable *H. influenzae* infection and/or in a vaccine to enhance lung clearance of a nontypeable *Haemophilus influenzae*, the as-filed application does not provide sufficient guidance and/or working examples for a skilled artisan to reasonably enable the claim invention. Hence one skilled in the Art will have to perform

extensive experimentation with each of these parameters to find the embodiments embraced by Applicant' claims, and as such, this experimentation would be considered undue.

Claim Rejections - 35 USC § 102 (a)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 60-67 are rejected under are rejected 35 U.S.C. §102(a) as being anticipated by May et al., (Proc Natl Acad Sci U S A. 2001 :3460-5).

The claims are drawn to an isolated polypeptide comprising an amino acid sequence having at least 99% identity to SEQ ID No: 2 or an immunogenic fragment or a polypeptide comprising at least 15 amino acids of SEQ ID No: 2. Claims are also drawn to fusion proteins comprising said polypeptides or said fragments.

May et al., teach the cloning and characterization of a complete genome sequence of a common avian clone of *Pasteurella multocida*, Pm70. The genome of Pm70 is a single circular chromosome of 2,257,487 base pairs in length. Genome-scale evolutionary analyses based on pairwise comparisons of 1,197 orthologous sequences between *P. multocida*, *Haemophilus influenzae*, and *Escherichia coli* suggest that *P. multocida* and *H. influenzae* diverged ≈270 million years ago and the γ subdivision of the proteobacteria radiated about 680 million years ago (May et al., PNAS, 2001, p. 3460, col. 1 paragraph 3) . May et al. teach a 222 amino acid

sequence of the complete strain Pm70 having 71.2% identity to SEQ ID NO:2. See Result 1, p. 1, on the attached search print out titled " us-10-500-530-2.rup". Absent evidence to the contrary, the isolated peptide of 222 amino acids inherently is immunogenic and comprises may regions with 100% identity to at least 15 contiguous fragments of SEQ ID NO:2. Thus, the *Pasteurella multocida*, Pm70 polypeptides of May are variants of SEQ ID NO:2 comprising a substitution, and deletion of one or more amino acids of at least 15 contiguous amino acids of SEQ ID No. 2.

Claim Rejections

Provisional *Rejection, Obviousness Type Double Patenting-No secondary Refence(s)*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 60-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-49 of U. S. of copending Application No. 10/484,156, filing date June 18, 2004. Although the conflicting

claims are not identical, they are not patentably distinct from each other because claims 27-38 of the '156 application and claims 60-67 of an isolated polypeptide comprising a member selected from the group consisting of: a) an amino acid sequence which has at least 85% identity to SEQ ID NO: 2, over the entire length of said sequence; and b) an immunogenic fragment of SEQ ID NO: 2, wherein the immunogenic fragment has substantially the same immunogenic activity as SEQ ID NO: 2.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 60-67 are not allowable

Claim 62 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nguyen Dave can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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